MICROFICHE

013377

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: May 17, 1999

MEMORANDUM

SUBJECT: **CHLORPYRIFOS-METHYL - Toxicology Endpoint Selection** - Report of the Hazard Identification Assessment Review Committee.

FROM: John Doherty, 5/19/99
Reregistration Branch 3
Health Effects Division 7509C

THROUGH: Jess Rowland, Co-Chair 5/17/99
Hazard Identification Assessment Review Committee
Toxicology Branch II, Health Effects Division 7509
And
Pauline Wagner, Co-Chair 5/17/99
Hazard Identification Assessment Review Committee
Health Effects Division 7509

TO: Steve Knizner, Branch Senior Scientist
Risk Characterization and Analysis Branch
Health Effects Division 7509C

PC Code: 059102

On March 30, 1999, the Health Effects Division's Hazard Identification Review Committee (HIARC) re-evaluated the toxicology data base of chlorpyrifos-methyl and to select toxicological endpoints for acute and chronic dietary as well as occupational and residential exposure risk assessments. This re-evaluation resulted from the re-review of some of the toxicology studies requested by HIARC at the September 30, 1997 meeting. The Committee's decisions are summarized below.

Committee Members in Attendance

Members present were: David Anderson, William Burnam, Virginia Dobozy, Pam Hurley, Mike Ioannou, Sue Makris, Nick Paquette, Kathleen Raffaele, Jess Rowland, P.V. Shah and Pauline Wagner. Data were presented by John Doherty of Reregistration Branch 3.

Also present were: Julianna Cruz and Steve Knizner, HED; Mark Hartman, SRRD; and Jonathan Chen and Steven Mulish, AD.

Data Presentation: & Report Preparation — John Doherty, Toxicologist — 5/19/99

I. INTRODUCTION

On September 30, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicology data base of chlorpyrifos-methyl and concluded that the Data Evaluation Records (DER's) prepared for toxicological studies did not provide critical information necessary to select toxicological endpoints for dietary and non-dietary (occupational/residential) exposure risk assessments and that these studies should be re-evaluated upon which the Committee will re-assess the database at a later date (*Memorandum:* J. Rowland to K. Whitby, dated October 20, 1997).

On May 5, 1998, (refer to report dated July 8, 1998 and HED Document No.: 012679) the HIARC re-evaluated the toxicology database of this chemical (based on the re-review of some of the toxicity studies) to select the toxicological endpoints for acute and chronic dietary as well as occupational and residential exposure risk assessments. In addition, the Committee also tried to re-assess the Reference Dose (RfD) established in 1986 for chronic dietary risk assessment and addressed the sensitivity of infants and children from exposure to chlorpyrifos-methyl as required by the Food Quality Protection Act of 1996. At this meeting it was again determined that the database was inadequate and appropriate studies were not available to select RfD doses and endpoints. This meeting also requested that additional studies be re-reviewed for reconsideration.

On March 30, 1999, the HIARC again re-evaluated the toxicology data base of chlorpyrifos-methyl. This re-evaluation resulted from either new submissions or the re-review of selected toxicology studies requested by HIARC at the September 30, 1997 meeting. The following presents an updating of the selection of the toxicity endpoints and other issues as concluded at the March 30, 1999 meeting.

II. HAZARD IDENTIFICATION

A. Acute Reference Dose

Study Selected: Developmental Toxicity §83-3a (870.3700).

MRID No.: 44680603

In the 1992 developmental toxicity study, pregnant Sprague-Dawley rats received oral administration of chlorpyrifos-methyl (96.9%) in corn oil at 0, 1, 12.5 or 50 mg /kg/day during gestation days 6 through 15. Post dosing salivation in 10% of the dams at 50 mg/kg/day was the only clinical sign of treatment. There were no treatment-related effects on survival, maternal body weight, or food consumption. Plasma, red blood cell and brain cholinesterase was measured on Gestation Day 20 (i.e., 5 days after the last dose). Red blood cell cholinesterase inhibition was seen in dams at 12.5 mg/kg/day (33% $p<0.01$) and at 50 mg/kg/day (47%) dose groups. Plasma cholinesterase was inhibited 8%, 8%, and 13% ($p < 0.01$) at 1, 12.5 and 50 mg/kg/day, dose groups, respectively, with

statistical significance only at the highest dose. Brain cholinesterase inhibition was seen only at the high dose ($p < 0.01$). For maternal toxicity, the NOAEL was 1 mg/kg/day and the LOAEL was 12.5 mg/kg/day based on red blood cell cholinesterase inhibition. No developmental toxicity was seen; there were no treatment-related increases in external, visceral or skeletal malformations or anomalies. For developmental toxicity, the NOAEL was 50 mg/kg/day (HDT); a LOAEL was not established.

Dose and Endpoint for Establishing the Acute RfD = Maternal NOAEL 1 mg/kg/day based on inhibition of red blood cell cholinesterase activity at 12.5 mg/kg/day (LOAEL).

Uncertainty Factor (UF): 1000 which includes, 10 x for inter-species extrapolation, 10 x for intra-species variability, and 10 x for FQPA considerations.

$$\textbf{Acute RfD} = \frac{\text{1 mg/kg/day (NOAEL)}}{\text{1000 (UF)}} = \textbf{0.001 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: The decrease in red blood cell cholinesterase was seen in dams at 12.5 mg/kg/day (LOAEL) on Gestation Day 20 which is 5 days after the last dose. However, unless demonstrated otherwise, HIARC considers that cholinesterase inhibition by an organophosphate would likely be the same or greater if the assessment was made following a single dose.

B. Chronic Reference Dose

Study Selected: Chronic Toxicity/Carcinogenicity Study -Rat §83-5 (870.4100)

MRID No.: 42269001

Executive Summary

In a combined carcinogenicity /chronic toxicity study (MRID 42269001), chlorpyrifos-methyl (95.2% a.i.) was administered to 60 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 0.05, 0.1, 1.0 and 50 mg/kg/day for 24 hours. Ten rats/sex/dose were sacrificed at 53 weeks.

Overt clinical signs of cholinesterase inhibition were not detected during the cageside observation periods. The high dose level male group showed a decrease in body weight gain of 12.8% and a statistically significant decrease in absolute body weight of 7.6% compared to controls. This decrease started at about day 68 and continued to the end of the study. In the females, the weight change at all dose levels versus the control was considered to be not toxicologically remarkable. No toxicologically significant changes in the urinalysis, hematological or clinical parameters were observed in treated animals at any dose level. Cholinesterase in both sexes was statistically significantly depressed at all time periods measured at the 1 mg/kg/day (plasma, 40-46% at 24 months) and 50 mg/kg/day (plasma, 85-94% at 24 months and brain, 37-47% at 24 months) dose levels versus the controls. RBC cholinesterase was sporadically depressed in both sexes at various time periods at 50 mg/kg/day.

At the terminal sacrifice, the adrenal cortex in the males showed a dose-related increase in the incidence of slight/moderate degree of diffuse vacuolation reaching 100% incidence at 50 mg/kg/day. In females, increases in adrenal vacuolation were seen only at 50 mg/kg/day with an incidence of 98%. This vacuolation was consistent with lipid accumulation of the zona fasciculata and an increase in the absolute and relative adrenal weight.

Statistically significant increase in adenomas of the pars distalis in the pituitary were seen in the females but the effect did not appear to be dose related. No other statistically significant increases in tumor incidence versus control were seen. **The LOAEL is 1 mg/kg/day, based on cholinesterase inhibition and pathological findings. The NOAEL is 0.1 mg/kg/day.**

This study in the rat is classified **Acceptable** and satisfies the guideline requirement for a carcinogenicity/chronic toxicity study (83-5) in rodents.

Dose and Endpoint for Establishing the Chronic RfD = NOAEL = 0.1mg/kg/day based on inhibition of plasma cholinesterase at 1 mg/kg/day (LOAEL).

Uncertainty Factor (UF): 100 (10 x for inter-species extrapolation and 10 x for intra-species variability) and 10 X for FQPA.

$$\textbf{Chronic RfD} = \frac{\text{0.1 mg/kg/day (NOAEL)}}{\text{1000 (UF)}} = \textbf{0.0001 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factor: This endpoint is supported by the 90-day study in dogs (MRID No. 44680601), the NOAEL was 0.1 mg/kg/day and the LOAEL was 10 mg/kg/day based on inhibition of plasma (50%) and red blood cell (25%) cholinesterase. Brain cholinesterase was inhibited only at 50 mg/kg/day.

C. Occupational/Residential Exposure

1. Dermal Absorption

Dermal Absorption Factor: 3%.

No dermal absorption studies are available with chlorpyrifos-methyl. Therefore, the HIARC extrapolated a dermal absorption factor by "bridging" data from oral and dermal studies conducted with chlorpyrifos.

For chlorpyrifos, in the oral rat developmental neurotoxicity study (MRID Nos. 44556901, 44661001), the LOAEL was 0.3 mg/kg/day and in the 21-day dermal toxicity study in rats, the LOAEL was 10 mg/kg/day (MRID No. 40972801). In both studies, the endpoint was cholinesterase inhibition. The resulting estimated dermal absorption is 3% (oral LOAEL 0.3 mg/kg/day ÷dermal LOAEL 10 x 100 = 3%).

2. Short-Term Dermal - (1-7 days)

Study Selected: Developmental Toxicity §83-3a

MRID No.: 44680603

Executive Summary: See Acute RfD.

Dose and Endpoint for Risk Assessment: Maternal NOAEL 1 mg/kg/day based on 33% ($p < 0.05$) inhibition of red blood cell cholinesterase at 12.5 mg/kg/day (LOAEL).

Comments about Study/Endpoint: .No dermal toxicity study is available in the database. Therefore, the HIARC selected the maternal NOAEL for this exposure scenario. The effects observed in this study are appropriate for this exposure period (1-7 days) of concern.

Since an oral value was selected, a dermal absorption factor of 3% should be used for route-to-route extrapolation.

This risk assessment is required.

3. Intermediate-Term Dermal (7 Days to Several Months)

Study Selected: Chronic Toxicity/Carcinogenicity Study -Rat §83-5

MRID No.: 42269001

Executive Summary: See Chronic RfD

Dose and Endpoint for Risk Assessment = NOAEL 0.1 mg/kg/day based on inhibition of plasma cholinesterase at 1 mg/kg/day at the 90-day interval.

Comments about Study/Endpoint: See chronic RfD discussion.

Since an endpoint from an oral study was selected, a dermal absorption factor of 3% should be used for route-to-route extrapolation.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Life-Time)

Study Selected: Chronic Toxicity/Carcinogenicity Study -Rat§83-5

MRID No.: 42269001

Executive Summary See Chronic RfD

Dose and Endpoint for Risk Assessment = NOAEL = 0.1mg/kg/day based on inhibition of plasma cholinesterase at 1 mg/kg/day (LOAEL).

Comments about Study/Endpoint/Uncertainty Factor: See Chronic RfD discussion.

Since an endpoint from an oral study was selected, a dermal absorption factor of 3% should be used for route-to-route extrapolation.

This risk assessment is required.

5. Inhalation Exposure (Any Time period).

Since there are no acceptable inhalation toxicity studies, the HIARC selected the oral doses used for the acute RfD (1 mg/kg, from the rat developmental toxicity study, MRID No.: 44680603) for short term inhalation exposure and the dose used for the chronic RfD (0.1 mg/kg/day, from the rat chronic feeding study, MRID No.: 42269001) for intermediate and long term inhalation risk assessments. These doses were also used for dermal exposure risk assessments. Inhalation exposure should be combined with the dermal exposure and the combined inhalation and dermal risk assessment calculated based on the combined oral equivalent dose as follows:

Step I. The inhalation exposure component (i.e., µg/lb a.i.) using a 100% absorption rate (default value), application rate, and the number of applications should be converted to an **equivalent oral dose (mg/kg/day)**

Step II. The dermal exposure component (i.e., mg/kg/day) using a 3% dermal absorption rate should be converted to an **equivalent oral dose.** This dose should then be combined with the converted oral dose in Step I.

Step III The combined **oral equivalent dose** from Step II should then be compared to the oral doses (1.0 mg/kg for short term exposure and 0.1 mg/kg/day for intermediate or long term exposure) to calculate the MOEs.

This risk assessment is required.

D. Margins of Exposure for Occupational/Residential Exposures

A Margin of Exposure (MOE) of 100 is adequate for occupational exposure. There are no registered residential uses at the present time.

E. Recommendation for Aggregate Exposure Risk Assessments

There are no registered residential uses at the present time. Therefore, aggregate risk assessment will be limited to food + water.

For **acute** aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

For **long-term** aggregate exposure risk assessment, combine the average exposure values from food + water and compare it to the chronic RfD.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

Executive Summary:

In a combined carcinogenicity /chronic toxicity study (MRID 42269001), chlorpyrifos-methyl (95.2% a.i.) was administered to 60 Fischer 344 rats/sex/dose in the diet at dose levels of 0, 0.05, 0.1, 1.0 and 50 mg/kg/day for 24 hours. Ten rats/sex/dose were sacrificed at 53 weeks. Overt clinical signs of cholinesterase inhibition were not detected during the cageside observation periods. The high dose level male group showed a decrease in body wright gain of 12.8% and a statistically significant decrease in absolute body weight of 7.6% compared to controls. This decrease started at about day 68 and continued to the end of the study. In the females, the weight change at all dose levels versus the control was considered to be not toxicologically remarkable. No toxicologically significant changes in the urinalysis, hematological or clinical parameters were observed in treated animals at any dose level. Cholinesterase activity in both sexes was statistically significantly depressed at all time periods at the 1 mg/kg/day (plasma, 40-46% at 24 months) and 50 mg/kg/day (plasma, 85-94% at 24 months and brain, 37-47% at 24 months) dose levels versus the controls. RBC cholinesterase was sporadically depressed in both sexes at various time periods at 50 mg/kg/day. At the terminal sacrifice, the adrenal cortex in the males showed a dose-related increase in the incidence of slight/moderate degree of diffuse vacuolation reaching 100% incidence at 50 mg/kg/day. In females, increases in adrenal vacuolation were seen only at 50 mg/kg/day with an incidence of 98%. This vacuolation was consistent with lipid accumulation of the zona fasciculata and an increase in the absolute and relative adrenal weight.

Statistically significant increase in adenomas of the pars distalis in the pituitary were seen in the females but the effect did not appear to be dose related. No other statistically significant increases in tumor incidence versus control were seen. **The LOEL is 1 mg/kg/day, based on cholinesterase inhibition and pathological findings. The NOEL is 0.1 mg/kg/day**.

This study in the rat is classified **Acceptable** and satisfies the guideline requirement for a carcinogenicity/chronic toxicity study (83-5) in rodents.

Discussion of Tumor Data: Statistically significance increases in adenomas of the *pars distalis* in the pituitary glands of female rats were observed. The incidences were: 13/50 (26%), 14/50 (28%), 27/50 (54%), 27/50 (54%) and 23/50 (46%) at 0, 0.05, 0.1, 1 and 50 mg/kg/day, respectively. The HIARC did not attribute this tumor increase to treatment because: 1) there was no dose response; 2) it was limited to only one sex (females); 3) the incidence was within the historical control; 4) the statistical increase was most likely due to the higher mortality in the control females (36/50, 72%) when compared to the mortality in the treated females (20/50, 40%); and 5) no evidence of carcinogenicity was seen with chlorpyrifos a structurally related organophosphate. Therefore, the HIARC concluded that the increase was not biologically significant and therefore not treatment-related.

Adequacy of the Dose Levels Tested: The highest dose tested was determined to be adequate to assess the carcinogenic potential of chlorpyrifos-methyl in male and female rats based on cholinesterase inhibition and decrease in body weight.

2. Carcinogenicity Study in Mice

EXECUTIVE SUMMARY: In an oncogenicity study (MRID 44680602), chlorpyrifos methyl (97.4% a.i., lot no. AGR 219561) was administered to groups of 52/sex pathogen free ICR Crj:CD-1® mice in the diet at concentrations of 0, 1, 5, 50, or 500 ppm for up to 78 weeks in the main study group. These concentrations resulted in a nominal compound intake for each concentration level of 0.0816, 0.418, 4.40, and 44.0 mg/kg/day for males; 0.0815, 0.403, 3.94, and 41.5 mg/kg/day for females for 1 ppm, 5 ppm, 50 ppm, and 500 ppm dietary mixtures, respectively. Satellite groups containing 44 mice per sex per group were fed the same diets for 26 and 52 weeks.

Systemic treatment related effects were noted at 500 ppm only. The mean **body weights** of males were decreased by 12% at 52 weeks and 17% at 78 weeks. Food consumption was slightly decreased in males during the first 12 weeks of the study, and the overall food efficiency of males was lower than the control group (control 1.2; 500 ppm, 1.0, NS). The total blood **cholesterol** was increased in males by 39% ($p < 0.05$) compared to the control at 26 weeks and in females by 45-79%, ($p < 0.05$ or 0.01) at all time points. Increased incidences of **fatty changes in centrilobular hepatocytes** were seen in males killed at 52 weeks (500 ppm, 75%; 25% of controls; $p < 0.01$), in main study males (500 ppm, 40%; controls, 18%, $p < 0.01$), in females killed at 52 weeks (500 ppm, 71%; controls 4%, $p < 0.01$), and in main study females (500 ppm, 40%; controls, 6%, $p < 0.01$). The incidence of diffuse hepatocellular fatty change was statistically increased in main study females *only* at 50 ppm (50 ppm 15%; control 2%, $p < 0.05$) and was marginally ($p = 0.07$) increased at 5 ppm. A significantly increased incidence of **kidney tubular atrophy** was seen in main study males (500 ppm, 60%; controls 34%, $p < 0.01$). The incidence of kidney tubular atrophy was marginally but not statistically significantly increased at 50 ppm ($p = 0.08$) in main study males. **Swelling of adrenal cortical cells** occurred in 42% ($p<0.01$) of main study and 25% ($p < 0.01$) of 52-week interim sacrifice male mice but did not occur in any animals fed the lower doses or the control groups. **The LOAEL for systemic effects is 500 ppm for both sexes (44.0 mg/kg/day for males and 41.5 mg/kg/day for females)**

based on histopathologic lesions in the liver, kidney, and adrenal glands. The NOAEL is 50 ppm (4.40 mg/kg/day for males and 3.94 mg/kg/day for females).

Cholinesterase from plasma and red blood cells was moderately inhibited at 50 ppm by 47-70% ($p < 0.01$ or < 0.05) in males and by 31-75% ($p < 0.01$ or < 0.05) in females and severely inhibited at 500 ppm by 93-96% ($p < 0.01$) in males and by 87-97% ($p < 0.01$) in females at all time points (26, 52, and 78 weeks). Brain cholinesterase was significantly decreased by 53-64% ($p < 0.01$) in 500-ppm group males and by 45-50% ($p < 0.01$) in 500-ppm group females at all time points. At 50 ppm, brain cholinesterase was statistically decreased in males (14%, $p < 0.05$) only at week 78, and in females a statistical decrease (25%, $p < 0.01$) was seen only at week 52. **The LOAEL for inhibition of cholinesterase is 50 ppm for both sexes (4.40 mg/kg/day for males and 3.94 mg/kg/day for females). The NOAEL is 5 ppm (0.418 mg/kg/day for males and 0.403 mg/kg/day for females).**

Treatment for up to 78 weeks with chlorpyrifos methyl did not result in a significant increase in the incidence of neoplastic lesions at any site. The animals were adequately dosed as evidenced by decreased cholinesterase at 50 ppm and treatment-related microscopic lesions in both sexes at 500 ppm.

This oncogenicity study in the mice is **Acceptable** and does satisfy the guideline requirement for an oncogenicity study (83-2b) in mice.

Discussion of Tumor Data: No evidence of carcinogenicity was seen.

Adequacy of the Dose Levels Tested: The highest dose tested was determined to be adequate to assess the carcinogenic potential of chlorpyrifos-methyl in male and female rats based on cholinesterase inhibition and decrease in body weight.

3. Classification of Carcinogenic Potential

The HIARC as of the March 30, 1999 meeting classified chlorpyrifos-methyl as "not likely to be a human carcinogen" based on the lack of evidence of carcinogenicity in male and female mice and male and female rats.

IV. MUTAGENICITY

The following table illustrates the mutagenicity data base for studies classified as ACCEPTABLE.

Study Type	Comments
Bacterial Mutagenicity (Ames test). MRID No.: 41887601.	No evidence mutagenic effect ± metabolic activation (S9) at dose levels up to 10,000 μg/plate.

Study Type	Comments
In vitro cytogenetic assay in CHO cells. MRID No.: 00154130.	-No evidence of a clastogenic effect in the absence of metabolic activation 4 to 40 μg/mL. -In the presence of metabolic activation (S9) and at 15 and 50 μg/m L chlorpyrifos-methyl was determined to be positive clastogenic in vitro.
In vitro gene mutations in the CHO/HGPRT. MRID No.: *00146053. (1985 study).*	-No evidence of mutagenic effects ± metabolic activation (S9).
In vivo mouse micronucleus assay. MRID No.: 00145108.	-No evidence of clastogenic effects at dose levels up to 1460 mg/kg.
In vitro unscheduled DNA synthesis in rat primary hepatocytes.	-No evidence of genotoxic response at dose levels up to 32.26 μg/mL.

V. FQPA CONSIDERATIONS

1. Neurotoxicity

A. Studies in Hens for Organophosphate Induced Delayed Type Neurotoxicity.

I. Acute Study (series 81-7, 1979 study).

The acute delayed neurotoxicity study in hens was classified as **unacceptable** and **not UPGRADABLE** (MRID No.: 00029503). The Committee determined that the equivocal nature of the histopathological findings should be considered tentatively positive for regulatory purposes until the weight of the evidence from other studies demonstrates otherwise. **Due to the equivocal nature of the results of the available study a repeat study with measurement of neurotoxic esterase (NTE) is required.**

ii. Subchronic Study (series 82-6, 1984 study).

In a range-finding study (Accession No.: 072888), White Leghorn hens were given chlorpyrifos-methyl in corn oil at doses of 0, 50, 100, 250, 500, 750, or 1000 mg/kg/day, 5 days/week for 4 weeks. The high dose was subjected to histopathological evaluation of brain, spinal cord, and peripheral nerves. Slight to moderate ataxia and CNS depression accompanied by substantial weight loss were observed at 750 and 1000 mg/kg/day. At the 1000 mg/kg/day, 2/5 hens died. No microscopic lesions indicative of delayed neurotoxicity were seen at 1000 mg/kg/day.

In a subchronic delayed neurotoxicity study (Accession No.: 0072888), chlorpyrifos-methyl in corn oil was administered by gavage at dose levels of 0, 5, 50 or 500 mg/kg/day, 5 days/week for a total of 65 doses to White Leghorn (9 months old) hens. No clinical signs of delayed neurotoxicity were seen at any dose level. A significant decrease in body weight as well a decrease in egg production was seen in hens at 500 mg/kg/day. At 500 mg/kg/day,

the lesions reported were very slight axonal degeneration in 1 to 4 hens and very slight focal gliosis in 1 to 6 hens. Although, there was no dose-response, the severity of the changes among treated hens were greater than those observed for the vehicle (corn oil) controls but less than those observed for the positive (TOCP) controls. They were similar in nature to the background neuropathological changes reported in the literature for white leghorn hens. The reviewer's conclusion was that the study did not appear to induce histopathological lesions indicative of delayed neurotoxicity in hens.

B. Neurotoxicity Screening in Rats.

Data Gaps exists for acute and subchronic neurotoxicity studies in rats.

2. Developmental Toxicity

(I) Rat

In the 1992 developmental toxicity study, pregnant Sprague-Dawley rats received oral administration of chlorpyrifos-methyl (96.9%) in corn oil at 0, 1, 12.5 or 50 mg /kg/day during gestation days 6 through 15. Post dosing salivation in 10% of the dams at 50 mg/kg/day was the only clinical sign of treatment. There were no treatment-related effects on survival, maternal body weight, or food consumption. Plasma, red blood cell and brain cholinesterase was measured on Gestation Day 20 (i.e., 5 days after the last dose). Red blood cell cholinesterase inhibition was seen in dams at 12.5 mg/kg/day (33% $p<0.05$) and at 50 mg/kg/day (47%) dose groups. Plasma cholinesterase was inhibited 8%, 8%, and 13% at 1, 12.5 and 50 mg/kg/day, dose groups, respectively, with statistical significance only at the highest dose. Brain cholinesterase inhibition was seen only at 50 mg/kg/day ($p <0.05$). For maternal toxicity, the NOAEL was 1 mg/kg/day and the LOAEL was 12.5 mg/kg/day based on red blood cell cholinesterase inhibition. No developmental toxicity was seen; there was no treatment-related increase in external, visceral or skeletal malformations or anomalies. For developmental toxicity, the NOAEL was 50 mg/kg/day (HDT); a LOAEL was not established. This 1992 study was classified as **Acceptable/Guidelines** satisfies the Guideline requirement for a developmental toxicity study in rats.

An issue of possible increased susceptibility of the fetuses based on delayed ossification of the sternebrae in the 1973 rat developmental toxicity study (Accession No.: 242150, study classified as Unacceptable because of reporting deficiencies and lack of individual animal data) at all dose levels (50, 100 and 200 mg/kg/day) which had a percent incidence of 0.6%, 5%, 11% and 8% for the pups affected and 3%, 26%, 38% and 28% for litters affected (all dosed groups were statistically significantly different from the control) did not show a true dose response. The 1992 study (MRID No.: 44680603) did not list sternebrae with delayed ossification as variant. On the contrary there was actually reported a statistically significant increase in fetuses with normal sternebrae and a decrease in variant sternebrae (see Table 11 of MRID No.: 44680603). Thus, the issue of a possible increase in susceptibility of rat fetuses relative to maternal toxicity based on delayed ossification of the sternebrae is considered resolved since no similar effect was noted in a study classified as acceptable that demonstrated maternal toxicity at doses lower than any indications of developmental toxicity

in the pups.

(ii). Rabbit

There is no acceptable developmental toxicity study in the data base for chlorpyrifos-methyl.

3. Reproductive Toxicity

In a three generation reproduction study (MRID No. 00030757), Sprague-Dawley rats were fed diets containing chlorpyrifos-methyl at 0,1 or 3 mg/kg/day for three successive generations. The parental/ systemic LOAEL was 1 mg/kg/day based on decreases in plasma and red blood cell cholinesterase a NOAEL was not established. For reproductive toxicity, the NOAEL was >3 mg/kg/day (HDT); a LOAEL was not established. This study is classified as **unacceptable not UNGRADABLE** because of several deficiencies which include: lack of purity, stability and homogeneity data; the use of only two dose levels, the lack of rationale for dose level selection; and the lack of statistical analyses on reproductive and viability endpoints.

A multi generation reproduction study is considered a data gap until either a new study is submitted or the existing study is upgraded.

4. Determination of the Need for a Developmental Neurotoxicity Study

There are unacceptable acute neurotoxicity studies in hens for delayed type neurotoxicity (series 81-7), developmental (rabbit, 83-3) and reproductive toxicity (83-4) in the rat studies. There are no acute (series 81-8) or subchronic (series 82-7) neurotoxicity screen studies in rats. The developmental neurotoxicity study is considered a data gap until completion of the data gaps for the series 81-7, 81-8, 82-7, 83-3 (rabbit) and 83-4 studies at which time the need for this study will be reevaluated.

5. Determination of Susceptibility

The HIARC could not make a determination on the increased susceptibility to infants and children (as required by FQPA) to chlorpyrifos-methyl due to the inadequate toxicology data base.

6. Recommendation to the FQPA Safety Factor Committee

The FQPA Safety Factor Committee, has determined that the additional **10x factor** for increased susceptibility to infants and children should be **retained** (FQPA Safety Factor Recommendations for the Organophosphates dated August 6, 1998).

VI. HAZARD CHARACTERIZATION

Chlorpyrifos-methyl is an organophosphate insecticide (O,O - dimethyl O-(3,5,6-trichloro-2-pyridyl)phosphorothioate) and its toxicity profile includes signs and symptoms typical of other organophosphates that inhibit cholinesterase. Thus, inhibition of plasma and/or red blood cell (RBC) cholinesterase was established as the critical endpoint for risk assessment. The dose levels selected for risk assessment did not show classical signs of cholinergic symptoms which were evident only at higher doses. Other systemic toxicity included body weight loss, decreased food consumption, liver, kidney and adrenal pathology. The potential for chlorpyrifos methyl to induce delayed type neurotoxicity remains open because the acute study was considered equivocal and a repeat acute study is being requested. A subchronic hen study did not indicate delayed type neuropathy in hens at dose levels up to and including 500 mg/kg/day. Neither the rat or the mouse carcinogenicity studies were interpreted as being positive for induction of neoplasia and HIARC has classified chlorpyrifos methyl as "not likely to be a human carcinogen". Developmental toxicity assessment is considered incomplete because there is only a rat study but no acceptable rabbit (or second species) study and there is no acceptable multi-generation reproduction study. Since the developmental toxicity data base is incomplete the assessment for increased susceptibility to fetuses and neonates is also incomplete. There is also no general metabolism study that adequately assess the uptake, distribution, retention and excretion or identification of metabolites. The mutagenicity data base conforms to current standards and was noted to be positive only in an *in vitro* cytogenic assay in the presence of metabolic activation.

VII. DATA GAPS

Currently there are data gaps for the following studies. Inclusion of the study as a data gap below implies that there is currently no acceptable study for the listed study type.

§ 81-1 (870.1100)	Acute oral toxicity-Rat
§ 81-2 (870.1200)	Acute dermal toxicity -Rabbit
§ 81-3 (870.1300)	Acute inhalation study- Rat
§ 81-4 (870.2400)	Primary ocular irritation-Rabbit
§ 81-5 (870.2500)	Primary dermal irritation-Rabbit
§ 81-6 (870.2600)	Dermal sensitization study- Guinea pigs
§ 81-7 (870.6100)	Delayed neurotoxicity study - Hens
§ 81-8 (870.6200)	Acute neurotoxicity study - Rat
§ 81-2 (870.3200)	Subchronic dermal toxicity study - Rat or Rabbit
§ 82-4 (870.3465)	Subchronic inhalation study -Rat
§ 82-7 (870.6200)	Subchronic neurotoxicity study -Rat
§ 83-1 (870.4100)	Chronic toxicity-Dog
§ 83-3b(870.3700)	Prenatal developmental neurotoxicity study - Rabbit
§ 83-4 (870.3800)	Two-generation reproduction study - Rat
§ 83-6 (870.6300)	Developmental neurotoxicity study -Rat
§ 85-1 (870.7485)	General metabolism-Rat
§ 85-2 (870.7600)	Dermal Absorption

VIII. ACUTE TOXICITY

Acute Toxicity of Chlorpyrifos-methyl

Guideline No.: and Study Type	MRID #	Results	Tox Category
81-1. (870.1100) Acute Oral	242152	LD_{50} in corn oil: = 2140 (1530-2990) mg/kg for males = 1090 (694-1710) mg/kg for females [Note: 1969 Supplementary study]	III
81.2. (870.1200) Acute Dermal	242152	LD_{50} > 2000 mg/kg. [Note: 1964 MINIMUM study]	III
81.3. (870.1300) Acute Inhalation		No valid study with technical grade.	
81.4. (870.2400) Primary Ocular	242152	Slight irritation in all eyes. Clearing 5/6 rabbits in seven days. [Note: 1974 MINIMUM study]	III
81.5. (870.2500) Primary Dermal	242152	No modern study. Classified as having irritation in 2/3 rabbits on days 4-7 exposure. [Note: 1964 MINIMUM study]	III
81.6. (870.2500) Sensitization		No study with technical material.	
81.7. (870.6100) Neurotoxicity - hens	0029503	Study is classified as UNACCEPTABLE- *not* UNGRADABLE. A repeat study is required to resolve the equivocal nature of the results.	
81.8 (870.6200) Neurotoxicity screen - rats		No Study.	

IX. SUMMARY OF TOXICOLOGIC ENDPOINT SELECTION

The doses and toxicologic endpoints selected for various exposure scenarios are summarized below:

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary General Population Including Infants and Children	NOAEL= 1 mg/kg/day	Inhibition of red blood cell cholinesterase.	Rat developmental toxicity (MRID No.: 44680603
	UF = 100	**Acute RfD = 0.01 mg/kg**	
Chronic Dietary	NOAEL= 0.1 Mg/kg/day	Inhibition of plasma cholinesterase.	Chronic/Carcinogenicity feeding study in rats (No.: 42269001)
	UF = 100	**Chronic RfD = 0.001 mg/kg/day**	
Dermal Absorption	3% based on comparison of the oral and dermal toxicity studies with chlorpyrifos using a common species and endpoint.		
Short-Term (Dermal/ Inhalation)	Oral NOAEL= 1 Mg/kg/day	Inhibition of red blood cell cholinesterase.	See Acute Dietary
Intermediate-Term (Dermal/ Inhalation)	Oral NOAEL = 0.1 Mg/kg/day	Inhibition of plasma cholinesterase noted at the 90-day measurement.	See Chronic Dietary
Long Term (Dermal/ Inhalation)	Oral NOAEL = 0.1 Mg/kg/day	Inhibition of plasma cholinesterase.	Chronic/Carcinogenicity feeding study in rats (No.: 42269001)
Carcinogenicity	Classified as "not likely a human carcinogen." Carcinogenicity risk assessment is not appropriate.		